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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,412	08/15/2006	Yoko Yamaguchi	WAS-NEG-P1/2F09027-US-P	8924

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EXAMINER
PAK, JOHN D

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
01/20/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/595,412	YAMAGUCHI ET AL.	
	Examiner	Art Unit	
	John Pak	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11 and 13-15* is/are pending in the application.

4a) Of the above claim(s) *14 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-7, 11, 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 1, 4-7, 11, 13-15 are pending in this application.

Claims 14-15 stand withdrawn from further consideration as being directed to non-elected subject matter. Claims 1, 4-7, 11 and 13 will presently be examined to the extent that they read on the elected subject matter.

The terminal disclaimer filed on 10/15/2010 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on pending application 10/595,413 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-7, 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/096396 in view of Yamaguchi et al. (March 2002) and The Merck Index.

It is noted that U.S. Patent Application Publication 2004/0185113 (hereinafter, Mizushima et al.) is a 371 of the international application that published as WO 02/096396 in the Japanese language. Therefore, Mizushima et al. can serve as the English translation of WO 02/096396. ***All page or paragraph references hereinbelow are to said English translation of WO 02/096396***.

WO 02/096396 discloses encapsulating "a biologically active substance" with sparingly water-soluble calcium-containing inorganic microparticles such as calcium carbonate (paragraphs 0009 & 0015) by binding the active substance to the inside of the inorganic microparticles to provide slowing of active substance elution, i.e. sustained release, from the microparticles (paragraphs 0011 & 0016). The active substance should be capable of binding to calcium and is preferably negatively charged (paragraph 0013). The active substance includes low-molecular weight anticancer agents and various other active substance types (paragraph 0014). Preferred microparticle size is disclosed as 10 nm to 500 nm so that gaps in walls of blood vessels of cancer sites and other sites of interest can be passed through (paragraph 0016). “Altering the concentration of the inorganic matter, the concentration of the drug, the stirring speed, and the operating time and temperature control the size of the particles." (paragraph 0024). **In all the examples, a 1.3 to 1.0 molar ratio of calcium chloride to sodium carbonate was used.** See paragraphs 0034 to 0051. Fine particle size of 10 nm can be produced by enhancing stirring power (id.). The microparticles are prepared by (1) preparing an aqueous solution of calcium salts such as calcium chloride, (2) adding and mixing an aqueous solution of a biologically active substance, and (3) adding and mixing an aqueous solution of carbonate such as sodium carbonate to allow the biologically active substance to be encapsulated (paragraph 0021). In order to prevent aggregation of microparticles, addition of protein, acid

mucopolysaccharide, surfactant and mannitol to the reaction solution is taught (paragraph 0023; claim 14).

Yamaguchi et al.[1] disclose retinoid (e.g., all-trans retinoic acid, ATRA), as an essential lipophilic vitamin for growth, maintenance of vision, morphogenesis and normal differentiation of epithelial tissue, hematocytes and immunocompetent cells (page 1, first paragraph). ATRA forms micelles in aqueous solution, and a nanoparticulate core-shell structure in which calcium carbonate crystals were grown on the outer surface of the micelle is disclosed (page 1, first paragraph, lines 11-14). The ATRA-$CaCO_3$ formulation was prepared by gradual addition of $CaCl_2$ and $NaCO_3$ into the aqueous solution in which ATRA was previously allowed to form micelles. (page 1, second paragraph). The particles were hydrodynamically characterized as spherical particles with a diameter of approximately 125 to 164 nm (page 2, first paragraph).

The Merck Index is cited to establish that ATRA is a known antineoplastic agent (page 1414).

The difference between WO 02/096396 and the claimed invention is that WO 02/096396 does not explicitly disclose retinoic acid as the low-molecular weight active substance and that the average particle size of the encapsulated retinoic acid is 5 to 106.4 nm. However, the technology taught by WO 02/096396 for encapsulating "a biologically active substance" with sparingly water-soluble calcium carbonate by binding

[1] This document is in the Japanese language but applicant provided an English translation thereof. All references here are to the English translation.

an active substance to the inside of the inorganic microparticles to provide sustained release from the microparticles is widely applicable to diverse active substances; and the secondary reference by Yamaguchi et al. is evidence that said technology would have been used to provide sustained release of retinoic acid. Not only is ATRA a well-known antineoplastic agent and thus suitable as an active substance in WO 02/096396, three of the inventors of WO 02/096396 later disclosed in the Yamaguchi et al. article the use of their encapsulating technology in encapsulating the water-insoluble ATRA.

Use of a surfactant in the reaction mixture is taught by WO 02/096396 as discussed above and specific choice of nonionic surfactant such as the well-known Tween or polysorbate surfactants (instant claims 7 and 10) and common solvent such as ethanol would have been routine optimization to form suitable micelles of water-insoluble ATRA. The claimed ratio of halide to carbonate is actually taught by WO 02/096396 as already discussed above. The step of adjusting the average particle size to 5-106.4 nm would have been obvious for the benefit of passing through the walls of blood vessels, as disclosed by WO 02/096396 (paragraph 0016), wherein increased stirring power has been taught for reducing to 10 nm (paragraph 0024).

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Applicant's amendments and arguments relative hereto, filed on 10/15/2010, have been given due consideration but they were deemed unpersuasive for the reasons set forth below.

Applicant argues the absence of specific disclosure of nonionic surfactant and adding the surfactant before adding calcium halide or acetate. Use of a nonionic surfactant in the reaction solution is not explicitly taught by WO 02/096396 but use of a surfactant in general is taught for the same purpose as in applicant's invention, i.e. to prevent aggregation of microparticles (paragraph 23; claim 14). Additionally, the active substance in WO 02/096396 is preferably negatively charged so as to bind to the calcium (paragraph 13). Consequently, one having ordinary skill in the art would have been motivated to select a nonionic surfactant so that it does not interfere with the binding of the negatively charged ATRA with the positively charged calcium.

As for the order/timing of adding the nonionic surfactant to the retinoic acid before adding calcium halide or acetate, WO 02/096396 teaches adding the surfactant to the reactant solution (claim 14). To the ordinary skilled artisan, this would have represented only two practical choices: add the surfactant to the calcium halide or acetate solution; or add the surfactant to the retinoic acid solution. Adding the surfactant after the two reactant solutions have been mixed would have produced the calcium-bound retinoic acid, and such order/timing would have been contrary to the purpose of preventing aggregation during production in WO 02/096396. Given only two alternatives, it would have been obvious to one of ordinary skill in the art to carry out

routine optimization of aggregation minimization to select the latter choice, adding the surfactant (nonionic for the reasons stated above) to the retinoic acid solution.

Further, applicant has admitted in the instant specification that previously reported and published retinoic acid-containing nanoparticles were made by adding a nonionic surfactant to retinoic acid in alkali-containing solution to form mixed micelles, to which a calcium coating is deposited (specification page 2, line 16 to page 3, line 24). The cited article herein by Yamaguchi et al. (March 2002) is one of the articles applicant acknowledged there. Therefore, at a minimum, such admission contradicts applicant's arguments here; and it would appear that selection and timing of adding nonionic surfactant would have been obvious for the reasons set forth above.

Specific choice of common solvent such as lower alcohol would have been routine optimization to form suitable micelles. Use of lower alcohol in aqueous alkali solution, which would increase the salt form of the acid, would have been suggested from the difficulty of formulating the insoluble retinoic acid with its lipophilic moiety. The step of adjusting the average particle size to 5-106.4 nm would have been obvious for the benefit of passing through the walls of blood vessels, as disclosed by WO 02/096396 (paragraph 0016), wherein increased stirring power has been taught for reducing to 10 nm (paragraph 0024), as discussed previously.

For these reasons, this ground of rejection is maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to John Pak whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/John Pak/
Primary Examiner, Art Unit 1616